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                 Derwent World Patents Index (DWPI) Revises Indexing
                 of Author Abstracts
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                 New FASTA Display Formats Added to USGENE and PCTGEN
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                 INPADOCDB and INPAFAMDB Enriched with New Content
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         FEB 16
                 and Features
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         FEB 16
                 INSPEC Adding Its Own IPC codes and Author's E-mail
                 Addresses
         APR 02
                 CAS Registry Number Crossover Limits Increased to
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      9
                 500,000 in Key STN Databases
         APR 02
                 PATDPAFULL: Application and priority number formats
NEWS 10
                 enhanced
NEWS 11
         APR 02
                 DWPI: New display format ALLSTR available
NEWS 12
         APR 02
                 New Thesaurus Added to Derwent Databases for Smooth
                 Sailing through U.S. Patent Codes
NEWS 13
         APR 02
                 EMBASE Adds Unique Records from MEDLINE, Expanding
                 Coverage back to 1948
         APR 07
                 CA/CAplus CLASS Display Streamlined with Removal of
NEWS 14
                 Pre-IPC 8 Data Fields
NEWS 15
         APR 07
                 50,000 World Traditional Medicine (WTM) Patents Now
                 Available in CAplus
NEWS 16
         APR 07
                 MEDLINE Coverage Is Extended Back to 1947
NEWS 17
         JUN 16 WPI First View (File WPIFV) will no longer be
                 available after July 30, 2010
         JUN 18
                 DWPI: New coverage - French Granted Patents
NEWS 18
NEWS 19
         JUN 18
                 CAS and FIZ Karlsruhe announce plans for a new
                 STN platform
NEWS 20
         JUN 18
                 IPC codes have been added to the INSPEC backfile
                  (1969-2009)
                 Removal of Pre-IPC 8 data fields streamline displays
NEWS 21
         JUN 21
                  in CA/CAplus, CASREACT, and MARPAT
NEWS 22
         JUN 21
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                 EMBASE Classic on STN
                 Introducing "CAS Chemistry Research Report": 40 Years
NEWS 23
         JUN 28
                 of Biofuel Research Reveal China Now Atop U.S. in
                 Patenting and Commercialization of Bioethanol
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=> s Sayers J?/AU

L1 385 SAYERS J?/AU

=> s 11 and growth(w)hormone

L2 22 L1 AND GROWTH(W) HORMONE

=> dup rem 12

PROCESSING COMPLETED FOR L2

L3 19 DUP REM L2 (3 DUPLICATES REMOVED)

=> s ARTYMIUK P?/AU

L4 363 ARTYMIUK P?/AU

=> s 14 and growth(w)hormone

L5 19 L4 AND GROWTH(W) HORMONE

=> dup rem 15

PROCESSING COMPLETED FOR L5

L6 16 DUP REM L5 (3 DUPLICATES REMOVED)

=> s ROSS R?/AU

L7 11282 ROSS R?/AU

=> s 17 and growth(w)hormone

L8 365 L7 AND GROWTH(W) HORMONE

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=> s 18 and ligand
L9 28 L8 AND LIGAND
=> dup rem 19
PROCESSING COMPLETED FOR L9
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      FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 14:57:00 ON 28 JUN 2010
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              385 S SAYERS J?/AU
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               22 S L1 AND GROWTH (W) HORMONE
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               19 DUP REM L2 (3 DUPLICATES REMOVED)
              363 S ARTYMIUK P?/AU
L4
L5
               19 S L4 AND GROWTH (W) HORMONE
               16 DUP REM L5 (3 DUPLICATES REMOVED)
L6
L7
            11282 S ROSS R?/AU
L8
              365 S L7 AND GROWTH (W) HORMONE
L9
               28 S L8 AND LIGAND
L10
               16 DUP REM L9 (12 DUPLICATES REMOVED)
=> dis ibib abs 13 1-19
     ANSWER 1 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2010:238593 CAPLUS
DOCUMENT NUMBER:
                              152:304118
TITLE:
                              Glucagon-like peptide I (GLP-1) fusions with
                              GLP-1-binding proteins, such as dipeptidyl peptidase
                              IV (DDP4), and antidiabetic uses thereof
                              Artymiuk, Peter; Ross, Richard; Sayers, Jon
INVENTOR(S):
PATENT ASSIGNEE(S):
                            Asterion Ltd., UK
SOURCE:
                              PCT Int. Appl., 72pp.
                              CODEN: PIXXD2
DOCUMENT TYPE:
                              Patent
LANGUAGE:
                              English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
     PATENT NO.
                      KIND DATE APPLICATION NO. DATE
      WO 2010020767 A2 20100225
                                                  WO 2009-GB2006 20090818
          W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
               CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
               ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,
               KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
               MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
          PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, DIJ, TT, TM
               ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
                                                     GB 2008-15248 A 20080821
US 2008-90813P P 20080821
GB 2009-7794 A 20090507
GB 2009 13003
PRIORITY APPLN. INFO.:
                                                                          A 20090810
                                                     GB 2009-13901
```

MARPAT 152:304118

OTHER SOURCE(S):

AB The inventors describe nucleic acid mols. that encode fusion polypeptides comprising GLP-1 (glucagon-like peptide I), or a receptor binding part thereof, linked directly or indirectly to a polypeptide that naturally binds GLP-1. In one embodiment GLP-1 is linked to an extracellular domain of a glucagon-like peptide-1 receptor (GLP-1 receptor, GLP1R). Alternative embodiments include the fusion of GLP-1 to inactivated dipeptidyl peptidase IV (DDP4, CD26) and optionally inactive adenosine deaminase (ADA), such as in the provided GLP1/DPP4/ADA fusion protein 10G1.

L3 ANSWER 2 OF 19 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:333182 BIOSIS DOCUMENT NUMBER: PREV200900334285

TITLE: Modified growth hormone fusion

polypeptides.

AUTHOR(S): Ross, Richard [Inventor]; Anonymous; Sayers, Jon

[Inventor]; Artymiuk, Peter [Inventor]

CORPORATE SOURCE: Sheffield, United Kingdom

ASSIGNEE: Asterion Limited

PATENT INFORMATION: US 07524649 20090428

SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (APR 28 2009) CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent LANGUAGE: English

ENTRY DATE: Entered STN: 27 May 2009

Last Updated on STN: 27 May 2009

AB The invention relates to chimeric polypeptides wherein said polypeptides

comprise a modified binding domain of growth hormone linked to a receptor binding domain of growth hormone receptor; and tandems/oligomers of said modified growth hormone binding domains.

L3 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:1048978 CAPLUS

DOCUMENT NUMBER: 151:307229

TITLE: Linker peptides including glycosylation sites for use

in fusion proteins

INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 185pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT NO.		KIND	DATE	APPL	ICATION NO	•	DATE
WO 20091039		 A1	20090827	 WO 2	 009-GB437		20090218
W: AE,	AG, AL,	AM, AC	, AT, AU,	AZ, BA,	BB, BG, E	H, BR, E	BW, BY, BZ,
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FI,	GB, GD,	GE, GH	, GM, GT,	HN, HR,	HU, ID, I	L, IN, I	S, JP, KE,
KG,	KM, KN,	KP, KR	, KZ, LA,	LC, LK,	LR, LS, I	T, LU, I	Y, MA, MD,
ME,	MG, MK,	MN, MW	, MX, MY,	MZ, NA,	NG, NI, N	O, NZ, C	M, PG, PH,
PL,	PT, RO,	RS, RU	, SC, SD,	SE, SG,	SK, SL, S	M, ST, S	SV, SY, TJ,
TM,	TN, TR,	TT, TZ	, UA, UG,	US, UZ,	VC, VN, Z	A, ZM, Z	ZW
RW: AT,	BE, BG,	CH, CY	, CZ, DE,	DK, EE,	ES, FI, F	R, GB, G	GR, HR, HU,
IE,	IS, IT,	LT, LU	, LV, MC,	MK, MT,	NL, NO, F	L, PT, F	RO, SE, SI,
SK,	TR, BF,	BJ, CF	, CG, CI,	CM, GA,	GN, GQ, G	W, ML, M	MR, NE, SN,
TD,	TG, BW,	GH, GM	, KE, LS,	MW, MZ,	NA, SD, S	L, SZ, I	Z, UG, ZM,

ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: GB 2008-2978 A 20080219

GB 2008-21076 A 20081119 GB 2009-539 A 20090114

OTHER SOURCE(S): MARPAT 151:307229

AB Peptide linkers that contain a glycosylation site and that can be used in the manufacture of fusion proteins that interact with membranes, e.g. fusion proteins of proteins and their cognate receptors. Glycosylation site

motif variants for use in linker peptides are described.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:791326 CAPLUS

DOCUMENT NUMBER: 151:132011

TITLE: Peptide fusion proteins for cancer therapy INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 36pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE DATE APPLICATION NO. _____ ____

 WO 2009081170
 A2
 20090702

 WO 2009081170
 A3
 20091203

 WO 2008-GB4279 20081224 W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.:

AB We disclose fusion proteins comprising a peptide comprising a binding domain for a receptor which is linked to a polypeptide comprising the binding domain to which said peptide binds.

L3 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:457596 CAPLUS

DOCUMENT NUMBER: 150:391157

TITLE: Protein and nucleotide sequences of modified

growth hormone polypeptides

INVENTOR(S): Artymiuk, Peter; Ross, Richard A.; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 44pp.

CODEN: PIXXD2
MENT TYPE: Patent

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

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                         A2 20090416 WO 2008-GB3056
     WO 2009047474
                                                                     20080910
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             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
             TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
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             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
             TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
                                            20080910

AK 2010-710215 20080910

US 2007-979010P P 20071010

GB 2007-19818 A 20071011

WO 2008-GB3056 W 2009001
     AU 2008309386 A1 20090416
                                          AU 2008-309386
     KR 2010067686
                               20100621
                                            KR 2010-710215
                         Α
PRIORITY APPLN. INFO.:
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AB The invention relates to modified growth hormone fusion proteins and dimers comprising said fusion proteins; nucleic acid mols. encoding said proteins and methods of treatment that use said proteins in the treatment of conditions that result from growth hormone excess. The protein and nucleotide sequences of modified growth hormone fusion protein for treatment of growth hormone related diseases.

L3 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:177456 CAPLUS

DOCUMENT NUMBER: 150:206809

TITLE: Insulin-like growth factor fusion proteins and

therapeutic uses thereof

INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 47pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PAT	CENT				KIN	D	DATE			APPL	ICAT				D.	ATE	
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		FΙ,	GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,
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EP	2190	874			A1		2010	0602		EP 2	-800	7761.	30		2	0800	805
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		SK,	TR,	AL,	BA,	MK,	RS										
ΙN	2010	KN00	777		А		2010	0521		IN 2	010-	KN77	7		2	0100	301

GB 2007-15213 A 20070806 US 2007-956333P P 20070816 WO 2008-GB2655 W 20080805 PRIORITY APPLN. INFO.:

This disclosure relates to insulin-like growth factor fusion polypeptides AB and nucleic acid mols. encoding said polypeptides. The fusion polypeptide comprises insulin-like growth factor, or active part thereof linked, directly or indirectly, to at least one insulin-like growth factor-binding domain of the insulin-like growth factor receptor. The invention also relates to methods of treating insulin-like growth factor deficiency related disorders with said polypeptides and nucleic acid mols. A method for preparing a hybridoma cell-line producing monoclonal antibodies which bind said polypeptides is also presented.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 7 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:115655 CAPLUS

150:161106 DOCUMENT NUMBER:

TITLE: Growth hormone fusion proteins

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

Asterion Limited, UK PATENT ASSIGNEE(S): SOURCE: PCT Int. Appl., 41pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATEN	IT NO.			KIN:		DATE				LICAT					ATE	
WO 20	09013	461				2009	0129								0080	716
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	CA	., СН,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	, DM,	DO,	DZ,	EC,	EE,	EG,	ES,
	FI	, GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	, HU,	ID,	IL,	IN,	IS,	JP,	ΚE,
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We disclose growth hormone fusion proteins that have AΒ increased in vivo stability and activity; nucleic acid mols. encoding said proteins and methods of treatment of growth hormone deficiency that use said proteins. This disclosure relates to the biol. actions of a ligand-receptor fusion (LR-fusion) of GH with its extracellular domain receptor. Such a genetically engineered LR-fusion protein was purified from mammalian cell culture. In rats the LR-fusion

had a 300-times reduced clearance compared to native GH and single administration promoted growth for 10 days far superior to that seen with native GH. The reduced clearance is reproducible in a primate model. The LR-fusion forms a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone as occurs naturally with GH and its binding protein. A recombinant gene encoding human GH linked to the A & B domains of the GHR extracellular domain (exGHR1-238) via a flexible (Gly4Ser)4 linker, was generated (Fig. 1 c).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 19 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:137246 BIOSIS DOCUMENT NUMBER: PREV200900137246

TITLE: Fusion protein comprising growth hormone

and growth hormone receptor.

AUTHOR(S): Ross, Richard [Inventor]; Anonymous; Artymiuk, Peter

[Inventor]; Sayers, Jon [Inventor]

CORPORATE SOURCE: Sheffield, United Kingdom

ASSIGNEE: Asterion Limited

PATENT INFORMATION: US 07446183 20081104

SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (NOV 4 2008) CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent LANGUAGE: English

ENTRY DATE: Entered STN: 18 Feb 2009

Last Updated on STN: 18 Feb 2009

AB This invention relates to agents which bind to cell surface receptors; methods to manufacture said agents; therapeutic compositions comprising said agents; and screening methods to identify novel agents.

L3 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2008:352889 CAPLUS

DOCUMENT NUMBER: 148:347917

TITLE: Growth factor chimeric protein for use in non-human

animals

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 36pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PAT	TENT	NO.			KIN:	D	DATE			APPL	ICAT	ION :	NO.		D.	ATE	
	2008 2008		59		A2 A3		 2008 2008		•	WO 2	007-				2	0070	913
NO.	W:	AE, CH, GB, KM, MG, PT,	AG, CN, GD, KN, MK, RO,	CO, GE, KP, MN, RS,	AM, CR, GH, KR, MW, RU,	AT, CU, GM, KZ, MX, SC,	AU, CZ, GT, LA, MY, SD,	AZ, DE, HN, LC, MZ, SE,	DK, HR, LK, NA, SG,	DM, HU, LR, NG, SK,	DO, ID, LS, NI, SL,	DZ, IL, LT, NO, SM,	EC, IN, LU, NZ, SV,	EE, IS, LY, OM,	EG, JP, MA, PG,	ES, KE, MD, PH,	FI, KG, ME, PL,
	RW:	AT, IS, BJ,	BE, IT, CF,	BG, LT, CG,	CH, LU, CI,	CY, LV, CM,	CZ, MC, GA,	UZ, DE, MT, GN,	DK, NL, GQ,	EE, PL, GW,	ES, PT, ML,	FI, RO, MR,	FR, SE, NE,	SI, SN,	SK, TD,	TR, TG,	BF, BW,

BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

US 20090270325 A1 20091029 US 2009-441361 20090319 PRIORITY APPLN. INFO.: GB 2006-18082 A 20060914 WO 2007-GB3453 W 20070913

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB We describe a chimeric protein comprising a growth

hormone polypeptide linked to a polypeptide comprising the

extracellular binding domain of growth hormone

receptor; its use in enhancing the growth and metabolism of non-human animals and homodimers comprising said chimeric protein.

L3 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2007:1303035 CAPLUS

DOCUMENT NUMBER: 147:535195

TITLE: Fusion protein composed of circularly permuted

growth hormone antagonist GHCP07C,

extracellular domain of receptor, and human modified

prolactin, and its use in construction of

pharmaceutical compositions for treating disorders

INVENTOR(S): Pradhananga, Sarbendra; Sayers, John; Ross,

Richard; Artymiuk, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 46pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA'	TENT :	NO.			KIN:		DATE			APPL	ICAT	ION 1	NO.		D.	ATE	
WO	2007	 1289	 79							 WO 2	007-	 GB12	 85		2	 0070	405
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	ΑZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,
		GD,	GE,	GH,	GM,	GΤ,	HN,	HR,	HU,	ID,	ΙL,	IN,	IS,	JP,	KE,	KG,	KM,
		KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	MG,	MK,
		MN,	MW,	MX,	MY,	MZ,	NΑ,	NG,	NΙ,	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,
							VC,										
	RW:										ES,						
											PT,						
											$ ext{ML}$,						
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	2648															0070	
EP	2004															0070	
	R:										ES,						
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	2009				_		2009				009-				_		
	1013										007-						
	2008										-800						
	2008						2008				008-		_		_		
	2008						2009				008-						
	2010				AI		2010	UZII			009-					0090	
IORIT	ı APP	ьN.	TNE.O	.:							006-					0060	
										WU Z	007-	2RT7	80		W 2	0070	400

AB The invention provides nucleic acid mols. encoding the circularly permuted human growth hormone GHCP07 and variants thereof, wherein variants contain amino acid changes at the receptor binding sites and acts as growth hormone receptor antagonists. The

invention also provides the amino acid sequences of GHCP07, and antagonist GHCP07C, wherein GHCP07C contains a C-terminal region of human growth hormone (GH) linked to a N-terminal region of GH, with a changes in amino acids at receptor binding sites, such as Glycine to Arginine at position 176. The invention further provides various fusion proteins comprised of: (a) at least two GHCP07C polypeptides linked in tandem; (b) extracellular binding domains of growth hormone receptor (GHR) linked to at least two GHCP07 polypeptides; (c) GHCP07C polypeptides linked to a human prolactin modified polypeptide (such as G129R PRL); and/or (d) GHCP07C-human modified prolactin fusions containing an extracellular domain of receptors, such as cytokine, GH, prolactin receptors. The invention was based on the general knowledge that the G129R mutation in PRL and G120R mutation in GH disrupt the structural integrity of the two receptor sites, and results in proteins acting as receptor antagonists. Still further, the invention provides: (a) nucleic acid mols. encoding the disclosed fusion proteins and their use in construction of vectors for recombinant protein production; and (b) the amino acid sequences of said extracellilar domains found in human GHR and the modified human prolactin (G129R). Finally, the invention provides for the use of the disclosed antagonists, and/or their fusion proteins, and/or their nucleic acids in construction of a pharmaceutical compn which can be use to treat various conditions, such as gigantism, acromegaly, cancer, diabetic retinopathy, diabetic nephropathy and/or other complications of diabetes and/or GH excess. In the examples, the invention presented mol. genetics methods used to generate circularly permutated growth hormone antagonists GHCP07BHis and GHCP07C, and showed that both proteins had antagonistic activity.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 19 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2007527470 MEDLINE DOCUMENT NUMBER: PubMed ID: 17721547

TITLE: A ligand-receptor fusion of growth

hormone forms a dimer and is a potent long-acting

agonist.

AUTHOR: Wilkinson Ian R; Ferrandis Eric; Artymiuk Peter J; Teillot

Marc; Soulard Chantal; Touvay Caroline; Pradhananga

Sarbendra L; Justice Sue; Wu Zida; Leung Kin C; Strasburger

Christian J; Sayers Jon R; Ross Richard J

CORPORATE SOURCE: School of Medicine and Biomedical Sciences, Royal

Hallamshire Hospital, University of Sheffield, Sheffield

S10 2JF, UK.

SOURCE: Nature medicine, (2007 Sep) Vol. 13, No. 9, pp. 1108-13.

Electronic Publication: 2007-08-26.

Journal code: 9502015. ISSN: 1078-8956. L-ISSN: 1078-8956.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200803

ENTRY DATE: Entered STN: 11 Sep 2007

Last Updated on STN: 13 Mar 2008 Entered Medline: 12 Mar 2008

AB Cytokine hormones have a short plasma half-life and require frequent administration. For example, growth hormone replacement involves daily injections. In common with other cytokines, the extracellular domain of the growth hormone

receptor circulates as a binding protein, which naturally prolongs the biological half-life of growth hormone. Here we have studied the biological actions of a ligand-receptor fusion of growth hormone and the extracellular domain of its receptor. The genetically engineered ligand-receptor fusion protein was purified from mammalian cell culture. In rats, the ligand-receptor fusion had a 300-times reduced clearance as compared to native growth hormone, and a single injection promoted growth for 10 d, far exceeding the growth seen after administration of native growth hormone. The ligand-receptor fusion forms a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone similar to the natural reservoir of growth hormone and its binding protein. In conclusion, a ligand-receptor fusion of cytokine to its extracellular receptor generates a potent, long-acting agonist with exceptionally slow absorption and elimination. This approach could be easily applied to other cytokines.

L3 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:104499 CAPLUS

DOCUMENT NUMBER: 144:219144

TITLE: Recombinant dimers of cytokine receptor-binding

domains linked by inflexible helical linkers for

modulation of cytokine signaling

INVENTOR(S): Artymiuk, Peter; Pradhananga, Sarbendra; Sayers,

John; Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PA'	TENT	NO.			KIN	D	DATE			APPL:	ICAT	ION 1	NO.		D.	ATE	
WO	2006 2006 2006	0108	91		A9		2006 2006 2006	0427		WO 2	005-	GB28	26		2	0050	718
		CN, GE, LC, NG, SL, ZA, CG, AT, IS, CF,	CO, GH, LK, NI, SM, ZM, CI, BE, IT, CG,	CR, GM, LR, NO, SY, ZW, CM, BG, LT, CI,	CU, HR, LS, NZ, TJ, SZ, GA, CH, LU,	CZ, HU, LT, OM, TM, BE, GN, CY, LV, GA,	AU, DE, ID, LU, PG, TN, CY, GQ, CZ, MC, GN,	DK, IL, LV, PH, TR, FR, GW, DE, NL, GQ,	DM, IN, MA, PL, TT, GR, ML, DK, PL, GW,	DZ, IS, MD, PT, TZ, IE, MR, EE, PT,	EC, JP, MG, RO, UA, IT, NE, ES, RO, MR,	EE, KE, MK, RU, UG, MC, SN, FI, SE, NE,	EG, KG, MN, SC, US, NL, TD, FR, SI, SN,	ES, KM, MW, SD, UZ, SI, TG GB, SK, TD,	FI, KP, MX, SE, VC, BF, GR, TR,	GB, KR, MZ, SG, VN, BJ, HU, BF, BW,	GD, KZ, NA, SK, YU, CF, IE, BJ, GH,
CA EP CN JP NZ	1010 2008 5532	KG, 2661 441 467 AT, IS, 1461 5072	KZ, 84 BE, IT, 6	MD, BG, LI,	RU, A1 A2 CH, LT, A T	TJ, CY, LU,	2006 2006 2007 CZ, LV, 2007 2008 2009	0202 0202 0411 DE, MC, 0808 0313	DK, NL,	AU 2 CA 2 EP 2 EE, PL, CN 2 JP 2	005- 005- 005- ES, PT, 005- 007-	2661 2575 7615 FI, RO, 8003 5231 5532	84 441 93 FR, SE, 0121 41	GB, SI,	2 2 2 GR, SK, 2 2	0050 0050 0050 HU, TR 0050 0050	718 718 718 718 IE, 718 718
	2391 2007				C2 A		2010 2007			RU 2 MX 2						0050 0070	

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KR 2007067678 A 20070628 KR 2007-703976 20070220 KR 891509 B1 20090406 IN 2007KN00631 A 20070706 IN 2007-KN631 20070221 KR 2009006221 A 20090114 KR 2008-729058 20081127 US 20090221477 A1 20090903 US 2009-658526 20090416 RITY APPLN. INFO.:

RITY APPLN. INFO.:

GB 2004-16687 A 20040727 GB 2005-2839 A 20050211
PRIORITY APPLN. INFO.:
                                                                                                                                                                   A 20050211
                                                                                                                   GB 2005-2839
                                                                                                                   WO 2005-GB2826 W 20050718
KR 2007-703976 A3 20070220
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

We disclose therapeutic proteins comprising at least two domains capable of binding to a cytokine receptor, wherein the domains are connected by a peptide linker, wherein the linker optionally comprises a rigid alpha helical region. These proteins may act as agonists or antagonists of cytokine signaling. Thus, growth hormone receptor-binding growth hormone fragments were dimerized using a rigid or semi-rigid linker. The rigid linker comprised the motif A(EAAAK)nA, with n = 1-5 preferred. These proteins were produced with transgenic E. coli. The growth hormone activity of these proteins was equal to or greater than growth hormone itself.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD

(3 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 13 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:34776 CAPLUS

DOCUMENT NUMBER: 142:127937

TITLE: Modified cytokine ligand polypeptides preparation,

screening, and uses thereof for treatment

Sayers, Jon; Artymuik, Peter; Ross, Richard INVENTOR(S):

Asterion Limited, UK PATENT ASSIGNEE(S): SOURCE: PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PA:	CENT 1	NO.			KINI)	DATE		j	APPL:	ICAT	ION 1	O.		D	ATE	
WO WO	2005 2005				A2 A3		2005		1	WO 2	004-0	GB28	27		2	0040	628
	W: RW:	CN, GE, LK, NO, TJ, BW,	CO, GH, LR, NZ, TM, GH,	CR, GM, LS, OM, TN, GM,	CU, HR, LT, PG, TR, KE,	CZ, HU, LU, PH, TT, LS,	AU, DE, ID, LV, PL, TZ, MW, RU,	DK, IL, MA, PT, UA, MZ,	DM, IN, MD, RO, UG, NA,	DZ, IS, MG, RU, US, SD,	EC, JP, MK, SC, UZ, SL,	EE, KE, MN, SD, VC, SZ,	EG, KG, MW, SE, VN, TZ,	ES, KP, MX, SG, YU, UG,	FI, KR, MZ, SK, ZA, ZM,	GB, KZ, NA, SL, ZM, ZW,	GD, LC, NI, SY, ZW
CA EP EP	2568 1639 1639	SI, SN, 859	SK, TD,	TR, TG	BF, A1 A2	ВJ,	GR, CF, 2005 2006 2010	CG, 0113 0329	CI,	•	GA,	GN, 2568	GQ, 859	GW,	ML,	•	NE,
	R:	•	•	•	•		ES, TR,	•		•	•			NL,	SE,	MC,	PT,

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JP 2008504001 T 20080214 JP 2006-518330 20040628
AT 466880 T 20100515 AT 2004-743175 20040628
US 20070264234 A1 20071115 US 2007-561831 20070316
PRIORITY APPLN. INFO.: GB 2003-15182 A 20030628
WO 2004-GB2827 W 20040628
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The disclosed invention describes modified cytokine ligand polypeptides comprising a modified amino acid sequence which is a modification of the native cytokine amino acid sequence of said ligand, wherein the native N terminal and C terminal amino acid residues of the native polypeptide are linked, directly or indirectly, together, characterized in that said ligand is provided with alternative N terminal and C terminal amino acid residues and further wherein at least one binding domain for said ligand's cognate binding partner or receptor complex is disrupted. The authors describe the first embodiment of the growth hormone circular permutation GH CP01, with the N terminus Ile121 and the C terminus Glul18. The "old" termini of GH were linked by a 6 amino acid linker, formed by joining the "old" termini -3 amino acids from the first helix at the N terminus and +3 residues for the last helix at the C terminus. E. coli cells were used as the expression system. Also described are alternative approaches to construct circular permutations of GH.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD

(2 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:878488 CAPLUS

DOCUMENT NUMBER: 141:344597

TITLE: Chimeric proteins containing cytokine receptor binding

domain and glycosylphosphatidylinositol anchor and

their therapeutic uses

INVENTOR(S): Ross, Richard; Sayers, Jon; Artymiuk, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

	TENT				KIN	D	DATE				_	ION I			D.	ATE		
WO	2004	0901	35				2004 2005		,			GB15			2	0040	407	
WO	W:	ΑE,	AG,	AL,	AM,	AT,	AU, DE,	AZ,	•	,	,	•	•	,	•	•	•	
		GE,	GH,	GM,	HR,	HU,	ID, LV,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,	
		NO,	NZ,	OM,	PG,	PH,	PL, TZ,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
	RW:	BW, BY,	,	,	,	•	MW, TJ,	,	,	,	,	,	•	,	,	•	•	
					•		HU, CG,					•			•			
EP	1616	TD,			A2		2006	0118		EP 2	004-	7262	19		2	0040	407	
		•	SI,	LT,	LV,	FI,	ES, RO,	•	•	•	•	•	•	•	•	•	•	HR
JP	2007	5276	95		Τ		2007	1004	1	JP 2	006-	5061	14		2	0040	407	

US 20060205926 A1 20060914 US 2005-552388 20051007

US 7625998 B2 20091201

PRIORITY APPLN. INFO.: GB 2003-8088 A 20030409

GB 2003-24235 A 20031016 WO 2004-GB1572 W 20040407

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The present invention relates to polypeptides which comprise a

ligand-binding domain of a cytokine receptor fused with a signal sequence

for the attachment of glycosylphosphatidylinositol (GPI) anchors.

GPI-anchors are post-translational modifications to proteins that add qlycosylphosphatidylinositol which enable these proteins to anchor to the extracellular side of cell membranes. 1B1-GP1 was constructed, in which GH was linked through its C-terminus to the extracellular domain of the GH receptor and then linked to the GPI signal sequence. 1C1-GPI was also constructed, in which a tandem of GH was linked through the second GH C-terminus to the GPI signal sequence. The invention provides vectors and

CHO-K1 cells for expressing GHBP-GPI.

OS.CITING REF COUNT: THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD 1

(1 CITINGS)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 15 OF 19 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on T.3

STN

2004:225928 BIOSIS ACCESSION NUMBER: DOCUMENT NUMBER: PREV200400225966

Tandem fusions of growth hormone and

its G120R mutated antagonist retain biological activity and

demonstrate prolonged plasma half-life.

Pradhananga, S. L. [Reprint Author]; Wilkinson, I. [Reprint AUTHOR(S):

Author]; Haylor, J. [Reprint Author]; Rezaee, S. [Reprint

Author]; Artymiuk, P.; Sayers, J.; Ross, R. J. M.

[Reprint Author]

Department of Clinical Sciences, Sheffield University, CORPORATE SOURCE:

Sheffield, UK

Growth Hormone & IGF Research, (April 2004) Vol. 14, No. 2, SOURCE:

pp. 116. print.

Meeting Info.: Second International GH-IGF Symposium.

Queensland, Australia. April 18-22, 2004.

ISSN: 1096-6374 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 21 Apr 2004

Last Updated on STN: 21 Apr 2004

ANSWER 16 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:591215 CAPLUS

DOCUMENT NUMBER: 139:144956

TITLE: Ligand binding domains of cytokine which are linked

via flexible polypeptide linker and uses in therapy

Ross, Richard; Artymiuk, Peter; Sayers, Jon INVENTOR(S):

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

KIND PATENT NO. DATE APPLICATION NO. DATE

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WO 2003062276 A2 20030731
WO 2003062276 A3 20031016
                                               WO 2003-GB253
          W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
              CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
              GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
              LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
              PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
              UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
              KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
              FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
              BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
                                20030731 CA 2003-2510751 20030124
20041020 EP 2003-702702 20030124
     CA 2510751
EP 1468020
                           A1
                            A2
          R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
              IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HO, SR

JP 2005529583 T 20051006 JP 2003-562153 20030124

RU 2325400 C2 20080527 RU 2004-121969 20030124

MX 2004007160 A 20050331 MX 2004-7160 20040723

BR 2004003173 A 20060321 BR 2004-3173 20040730

US 20050214762 A1 20050929 US 2005-502344 20050511

PRIORITY APPLN. INFO.:

GB 2002-1679 A 20020125

WO 2003-GB253 W 20030124
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
     The invention relates to the provision of oligomeric polypeptides (dimers,
     trimers, etc) comprising the ligand binding domains of cytokines which are
     linked via flexible polypeptide linker mols. The linker mols. optionally
     comprise protease sensitive sites to modulate the release of biol. active
     cytokines when administered to a human or animal subject. The invention
     also relates to chemical crosslinkers wherein the chemical crosslinkers serve
t.o
     link the ligand binding domains. The chimeric cytokine can be used for
     treating acromegaly, gigantism, GH deficiency, Turners syndrome, renal
     failure, osteoporosis, diabetes mellitus, cancer, obesity, insulin
     resistance, hyperlipidemia, hypertension, anemia, autoimmune and
     infectious disease, inflammatory disorders including rheumatoid arthritis.
OS.CITING REF COUNT:
                         1
                                 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
                                  (1 CITINGS)
REFERENCE COUNT:
                                  THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
                                  RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
     ANSWER 17 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 2003:949911 CAPLUS
DOCUMENT NUMBER:
                          140:13709
TITLE:
                          Polypeptide having a plurality of modified
                           growth hormone receptor binding
                           domains from growth hormone, and
                           therapeutic use
INVENTOR(S):
                           Ross, Richard; Sayers, Jon; Artymuik, Peter
                         Asterion Limited, UK
PATENT ASSIGNEE(S):
                           Brit. UK Pat. Appl., 31 pp.
SOURCE:
                           CODEN: BAXXDU
DOCUMENT TYPE:
                           Patent
                           English
LANGUAGE:
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:
     PATENT NO. KIND DATE APPLICATION NO. DATE
     GB 2389115 A 20031203 GB 2003-20479 20011214
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GB 2389115	В	20050316		
GB 2384001	A	20030716	GB 2001-30052	20011214
GB 2384001	В	20040204		
AU 2008201889	A1	20080522	AU 2008-201889	20080430
PRIORITY APPLN. INFO.:			GB 2001-30052	A3 20011214
			AU 2002-366325	A3 20021206

AB A chimeric polypeptide having a first and a second modified growth hormone receptor binding domain from growth hormone wherein the modification may be a deletion, substitution or addition of at least one amino acid residue and the said binding domains are joined in tandem. The binding domain may be modified in one of either site 1 or site 2 or at both sites 1 and 2. Specific modifications of said sites are disclosed as are linkers, polynucleotides encoding said polypeptides, vectors, cells expressing said polypeptide and methods of expressing said polypeptides. Pharmaceutical compns. comprising said polypeptides and their uses in treating diseases such as giantism, acromegaly, cancer, diabetic retinopathy, nephropathy or complications are claimed. The polypeptide may have a plurality of modified binding domains, especially those modified at site 2.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:550165 CAPLUS

DOCUMENT NUMBER: 139:112729

TITLE: Chimeric growth hormone-

growth hormone receptor proteins and

therapeutic uses thereof

INVENTOR(S): Ross, Richard; Sayers, Jon; Artymuik, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK

SOURCE: Brit. UK Pat. Appl., 46 pp.

CODEN: BAXXDU

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT NO.	KIND DATE	APPLICATION NO.	
GB 2384001			
GB 2384001	B 20040204		
GB 2389115	A 20031203	GB 2003-20479	20011214
GB 2389115	B 20050316		
CA 2468439	A1 20030828	CA 2002-2468439	20021206
WO 2003070765	A2 20030828	WO 2002-GB5523	20021206
WO 2003070765	A3 20031127		
W: AE, AG, AL,	AM, AT, AU, AZ,	BA, BB, BG, BR, BY, BZ,	CA, CH, CN,
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		MC, NL, PT, SE, SI, SK,	, , ,
		GW, ML, MR, NE, SN, TD, AU 2002-366325	
		AU 2002-366325	20021206
	B2 20080424	TD 0000 006050	00001006
		EP 2002-806858	
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	1604965			20050406	CN	2002-824781		20021206
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	20050123558		A1 2	20050609	US	2005-498497		20050114
US	7524649		B2 2	20090428				
ZA	2006000149		A 2	20061025	ZA	2006-149		20060106
KR	2006106862		A 2	20061012	KR	2006-716929		20060823
KR	848802		B1 2	20080728				
KR	2007108254		A 2	20071108	KR	2007-721636		20070920
KR	879553		B1 2	20090122				
IN	2008KN01333		A 2	20081226	IN	2008-KN1333		20080402
AU	2008201889			20080522	AU	2008-201889		20080430
	20090239801			20090924	US	2009-389022		20090219
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A chimeric polypeptide comprising at least one modified binding domain of growth hormone (GH) and a ligand binding domain of growth hormone receptor (GHR) is claimed, wherein the modification is the addition, deletion or substitution of at least one amino acid. Said binding domain may be site 1 of growth hormone, site 2 of growth hormone or both sites of growth hormone. The binding domain of the growth hormone receptor may be the extracellular domain of GHR more preferably the C-terminal SD-100 domain. Nucleic acids encoding such polypeptides, expression vectors and cells expressing such vectors are also claimed. The use of such polypeptides in the preparation of pharmaceuticals and in the treatment of diseases including gigantism, acromegaly, cancer and diabetic conditions is also claimed. Alternatively claimed is a chimeric polypeptide comprising more than two modified growth hormone binding domains.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2010 ACS on STN
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ACCESSION NUMBER: 2001:924005 CAPLUS

DOCUMENT NUMBER: 136:49347

TITLE: Chimeric binding agent comprising cytokine, linker and

cytokine receptor and uses in modulating receptor

activity and therapy

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 79 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	CENT 1	NO.			KIN	D	DATE			APP	LICAT	ION 1	NO.		D	ATE	
	2001									WO	2001-	 GB26	 45		2	0010	618
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	2447				A1						2001-						
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	R:										, IT,	LI,	LU,	NL,	SE,	MC,	PT,
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											2002-						
										US	2003-	3114	/3		2	0030	718
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PRIORIT	APP.	LN.	TNF.O	.:						_	2000-	_	-			0000	-
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides a binding agent comprising a first part capable of binding a ligand binding domain of a receptor linked to a second part comprising a receptor binding domain wherein said binding agent modulates the activity of the receptor. The inventors link growth hormone (GH), through its C-terminal and a linker to the N-terminus of the SD100 domain of growth hormone receptor (GHR). By varying the length of the linker inventors define a mol. that has the flexibility to allow binding of GH through site 1 to full length receptor at the cell surface. The invention also relates to

methods, vectors and host cells for production of said chimeric binding agent.
OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD
(6 CITINGS)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL STNGUIDE SINCE FILE COST IN U.S. DOLLARS TOTAL ENTRY SESSION FULL ESTIMATED COST 84.76 84.98 DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL ENTRY SESSION CA SUBSCRIBER PRICE -12.75-12.75

FILE 'STNGUIDE' ENTERED AT 15:01:53 ON 28 JUN 2010

USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION. LAST RELOADED: Jun 25, 2010 (20100625/UP).

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(FILE 'HOME' ENTERED AT 14:56:38 ON 28 JUN 2010)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 14:57:00 ON 28 JUN 2010 385 S SAYERS J?/AU L1L222 S L1 AND GROWTH (W) HORMONE L3 19 DUP REM L2 (3 DUPLICATES REMOVED) 363 S ARTYMIUK P?/AU L4L5 19 S L4 AND GROWTH(W)HORMONE 16 DUP REM L5 (3 DUPLICATES REMOVED) L6 L7 11282 S ROSS R?/AU 365 S L7 AND GROWTH (W) HORMONE L8 L9 28 S L8 AND LIGAND L10 16 DUP REM L9 (12 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 15:01:53 ON 28 JUN 2010

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YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, BIOSIS, CAPLUS' - CONTINUE? (Y)/N:y

ANSWER 1 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2010:238593 CAPLUS

DOCUMENT NUMBER: 152:304118

TITLE: Glucagon-like peptide I (GLP-1) fusions with

GLP-1-binding proteins, such as dipeptidyl peptidase

IV (DDP4), and antidiabetic uses thereof

INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Ltd., UK SOURCE: PCT Int. Appl., 72pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PAT	ENT :	NO.			KIN	D	DATE			APPL	ICAT:	ION I	. O <i>l</i> .		D	ATE	
WO	2010	0207	 67		A2	_	2010	0225	1	WO 2	 009-	GB20)6		2	0090	818
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		ES,	FI,	GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,
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		PG,	PH,	PL,	PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	ST,	SV,
		SY,	ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HR,	HU,
		ΙE,	IS,	ΙΤ,	LT,	LU,	LV,	MC,	MK,	MT,	NL,	NO,	PL,	PT,	RO,	SE,	SI,
		SK,	SM,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,
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		ZM,	ZW,	ΑM,	ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ΤJ,	TM					
)RITY	APP	APPLN. INFO.:							(GB 2	008-	1524	8	Ž	A 2	0800	821

US 2008-90813P P 20080821 GB 2009-7794 A 20090507 GB 2009-13901 A 20090810

OTHER SOURCE(S): MARPAT 152:304118

AB The inventors describe nucleic acid mols. that encode fusion polypeptides comprising GLP-1 (glucagon-like peptide I), or a receptor binding part thereof, linked directly or indirectly to a polypeptide that naturally binds GLP-1. In one embodiment GLP-1 is linked to an extracellular domain of a glucagon-like peptide-1 receptor (GLP-1 receptor, GLP1R). Alternative embodiments include the fusion of GLP-1 to inactivated dipeptidyl peptidase IV (DDP4, CD26) and optionally inactive adenosine deaminase (ADA), such as in the provided GLP1/DPP4/ADA fusion protein 10G1.

L6 ANSWER 2 OF 16 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:333182 BIOSIS DOCUMENT NUMBER: PREV200900334285

TITLE: Modified growth hormone fusion

polypeptides.

AUTHOR(S): Ross, Richard [Inventor]; Anonymous; Sayers, Jon

[Inventor]; Artymiuk, Peter [Inventor]

CORPORATE SOURCE: Sheffield, United Kingdom

ASSIGNEE: Asterion Limited

PATENT INFORMATION: US 07524649 20090428

SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (APR 28 2009) CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent LANGUAGE: English

ENTRY DATE: Entered STN: 27 May 2009

Last Updated on STN: 27 May 2009

 ${\tt AB}$ The invention relates to chimeric polypeptides wherein said polypeptides

comprise a modified binding domain of growth hormone linked to a receptor binding domain of growth hormone receptor; and tandems/oligomers of said modified growth hormone binding domains.

L6 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:1048978 CAPLUS

DOCUMENT NUMBER: 151:307229

TITLE: Linker peptides including glycosylation sites for use

in fusion proteins

INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 185pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT N	Ο.			KIN)	DATE			APPL	ICAT	ION I	NO.		D	ATE	
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WO 20091	0396	55		A1		2009	0827	,	WO 2	009-	GB43	7		2	0090	218
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             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:
                                            GB 2008-2978
                                                                A 20080219
                                            GB 2008-21076
                                                                A 20081119
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GB 2009-539

A 20090114

OTHER SOURCE(S): MARPAT 151:307229

Peptide linkers that contain a qlycosylation site and that can be used in the manufacture of fusion proteins that interact with membranes, e.g. fusion proteins of proteins and their cognate receptors. Glycosylation site

motif variants for use in linker peptides are described.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 4 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:791326 CAPLUS

DOCUMENT NUMBER: 151:132011

Peptide fusion proteins for cancer therapy TITLE: INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK PCT Int. Appl., 36pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent English LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	TENT	NO.			KIN	D	DATE		-	APPL	ICAT	ION	NO.		D	ATE	
	2009 2009				A2 A3		2009 2009	-		WO 2	008-	GB42	79		2	0081	224
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		ME, MG, MK, PL, PT, RO, TM, TN, TR,				,	•	•	•	•	•	•	•	•	•	SY,	TJ,
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		RW: AT, BE, BG, IE, IS, IT,				,	,	,	,	,	,	,	,	,	,	,	SK, TD,
	TR, BF, BJ TG, BW, GH				•			•		•		•	•	•	•	•	,
PRIORIT	Y APP	•	•	,	KG,	KZ,	MD,	RU,		TM, GB 2	•	,	,		A 2	0071	224

AB We disclose fusion proteins comprising a peptide comprising a binding domain for a receptor which is linked to a polypeptide comprising the binding domain to which said peptide binds.

ANSWER 5 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:457596 CAPLUS

DOCUMENT NUMBER: 150:391157

TITLE: Protein and nucleotide sequences of modified

growth hormone polypeptides

INVENTOR(S): Artymiuk, Peter; Ross, Richard A.; Sayers,

Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 44pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	PATENT	NO.			KIN:	D	DATE			APPL	ICAT	ION 1	NO.		D.	ATE	
_ W	vo 200	90474	74		A2		2009	0416	,	WO 2	008-	GB30	56		2	0080	910
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		TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,
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A	AU 2008309386				A1		2009	0416		AU 2	008-	3093	86		2	0080	910
K	KR 2010067686				Α		2010	0621		KR 2	010-	7102	15		2	0080	910
PRIORI	IORITY APPLN. INFO.:			.:						US 2	007-	9790	10P]	P 2	0071	010
									1	GB 2	007-	1981	8	i	A 2	0071	011
									,	WO 2	008-	GB30	56	Ī	W 2	0080	910

AB The invention relates to modified growth hormone fusion proteins and dimers comprising said fusion proteins; nucleic acid mols. encoding said proteins and methods of treatment that use said proteins in the treatment of conditions that result from growth hormone excess. The protein and nucleotide sequences of modified growth hormone fusion protein for treatment of growth hormone related diseases.

L6 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:177456 CAPLUS

DOCUMENT NUMBER: 150:206809

TITLE: Insulin-like growth factor fusion proteins and

therapeutic uses thereof

INVENTOR(S): Artymiuk, Peter; Ross, Richard; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 47pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PAT		NT NO.			KIN	D	DATE			APPL	ICAT				D.	ATE	
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EP 2190874
                        A1 20100602 EP 2008-776130 20080805
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             SK, TR, AL, BA, MK, RS
                                           IN 2010-KN777 20100301
GB 2007-15213 A 20070806
     IN 2010KN00777 A 20100521
PRIORITY APPLN. INFO.:
                                            US 2007-956333P P 20070816
WO 2008-GB2655 W 20080805
    This disclosure relates to insulin-like growth factor fusion polypeptides
AΒ
     and nucleic acid mols. encoding said polypeptides. The fusion polypeptide
     comprises insulin-like growth factor, or active part thereof linked,
     directly or indirectly, to at least one insulin-like growth factor-binding
    domain of the insulin-like growth factor receptor. The invention also
    relates to methods of treating insulin-like growth factor deficiency
    related disorders with said polypeptides and nucleic acid mols. A method
     for preparing a hybridoma cell-line producing monoclonal antibodies which
     bind said polypeptides is also presented.
REFERENCE COUNT:
                        7
                             THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L6 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:115655 CAPLUS

DOCUMENT NUMBER: 150:161106

TITLE: Growth hormone fusion proteins

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 41pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA	TENT	NO.			KIN	D	DATE		,	APPL	ICAT	ION I	NO.		D.	ATE	
WO	2009	0134	61		A1		2009	0129		WO 2	008-	GB24	06		2	0080	716
	W:	ΑE,	AG,	AL,	AM,	ΑO,	ΑT,	ΑU,	ΑZ,	ΒA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,
		CA,	CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,
		FΙ,	GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KΕ,
		KG,	ΚM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,
		ME,	MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,
		PL,	PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	ST,	SV,	SY,	ТJ,
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	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HR,	HU,
		ΙE,	IS,	ΙT,	LT,	LU,	LV,	MC,	MT,	NL,	NO,	PL,	PT,	RO,	SE,	SI,	SK,
		TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,
		TG,	BW,	GH,	GM,	ΚE,	LS,	MW,	${ m MZ}$,	NA,	SD,	SL,	SZ,	ΤZ,	UG,	ZM,	ZW,
		ΑM,	ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ΤJ,	TM							
AU	2008	2789	07		A1		2009	0129		AU 2	008-	2789	07		2	0800	716
CA	2693	951			A1		2009	0129		CA 2	008-	2693	951		2	0800	716
EP	2170	943			A1		2010	0407		EP 2	008-	7759	45		2	0800	716
	R:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HR,	HU,
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		SK,	TR,	ΑL,	BA,	MK,	RS										
	2010										010-				2	0800	716
CN	1016	7950	4		Α		2010	0324		CN 2	008-	8002	1473		2	0091	222
ORIT	Y APP	LN.	INFO	.:						US 2	007-	9511.	22P	i	A 2	0070	720
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											008-0			Ţ	W 2	0800	716
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AB We disclose growth hormone fusion proteins that have increased in vivo stability and activity; nucleic acid mols. encoding said

proteins and methods of treatment of growth hormone deficiency that use said proteins. This disclosure relates to the biol. actions of a ligand-receptor fusion (LR-fusion) of GH with its extracellular domain receptor. Such a genetically engineered LR-fusion protein was purified from mammalian cell culture. In rats the LR-fusion had a 300-times reduced clearance compared to native GH and single administration promoted growth for 10 days far superior to that seen with native GH. The reduced clearance is reproducible in a primate model. The LR-fusion forms a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone as occurs naturally with GH and its binding protein. A recombinant gene encoding human GH linked to the A & B domains of the GHR extracellular domain (exGHR1-238) via a flexible (Gly4Ser)4 linker, was generated (Fig. 1 c).

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS REFERENCE COUNT: 6 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:137246 BIOSIS DOCUMENT NUMBER: PREV200900137246

Fusion protein comprising growth hormone TITLE:

and growth hormone receptor.

AUTHOR(S): Ross, Richard [Inventor]; Anonymous; Artymiuk,

Peter [Inventor]; Sayers, Jon [Inventor]

CORPORATE SOURCE: Sheffield, United Kingdom

ASSIGNEE: Asterion Limited

PATENT INFORMATION: US 07446183 20081104

Official Gazette of the United States Patent and Trademark SOURCE:

Office Patents, (NOV 4 2008) CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent LANGUAGE: English

ENTRY DATE: Entered STN: 18 Feb 2009

Last Updated on STN: 18 Feb 2009

This invention relates to agents which bind to cell surface receptors; AB methods to manufacture said agents; therapeutic compositions comprising said agents; and screening methods to identify novel agents.

ANSWER 9 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2008:352889 CAPLUS

DOCUMENT NUMBER: 148:347917

Growth factor chimeric protein for use in non-human TITLE:

animals

Ross, Richard; Artymiuk, Peter; Sayers, Jon INVENTOR(S):

PATENT ASSIGNEE(S): Asterion Limited, UK PCT Int. Appl., 36pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent English LANGUAGE:

FAMILY ACC. NUM. COUNT: 1

PATENT NO.	KIND DAT	E APPLI	ICATION NO.	DATE
WO 2008032059	A2 200)80320 WO 20	07-GB3453	20070913
WO 2008032059	A3 200)80508		
W: AE, AG, AL,	AM, AT, AU	J, AZ, BA, BB,	BG, BH, BR, BW,	BY, BZ, CA,
CH, CN, CO,	CR, CU, CZ	Z, DE, DK, DM,	DO, DZ, EC, EE,	EG, ES, FI,
GB, GD, GE,	GH, GM, GT	C, HN, HR, HU,	ID, IL, IN, IS,	JP, KE, KG,
KM, KN, KP,	KR, KZ, LA	A, LC, LK, LR,	LS, LT, LU, LY,	MA, MD, ME,
MG, MK, MN,	MW, MX, MY	, MZ, NA, NG,	NI, NO, NZ, OM,	PG, PH, PL,
PT, RO, RS,	RU, SC, SD), SE, SG, SK,	SL, SM, SV, SY,	TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA US 20090270325 A1 20091029 US 2009-441361 20090319 GB 2006-18082 PRIORITY APPLN. INFO.: A 20060914 WO 2007-GB3453 W 20070913

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

We describe a chimeric protein comprising a growth

hormone polypeptide linked to a polypeptide comprising the

extracellular binding domain of growth hormone

receptor; its use in enhancing the growth and metabolism of non-human animals and homodimers comprising said chimeric protein.

ANSWER 10 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2007:1303035 CAPLUS

DOCUMENT NUMBER: 147:535195

Fusion protein composed of circularly permuted TITLE:

growth hormone antagonist GHCP07C,

extracellular domain of receptor, and human modified

prolactin, and its use in construction of

pharmaceutical compositions for treating disorders

INVENTOR(S): Pradhananga, Sarbendra; Sayers, John; Ross, Richard;

Artymiuk, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 46pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PA	TENT	NO.			KIN	D	DATE			APPL	ICAT	ION I	NO.		D	ATE	
WC	2007	1289	 79		A1	_	2007	1115		 WO 2	007-	 GB12	 85		2	0070	405
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,
		GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,
		KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	MG,	MK,
		MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW						
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,
		IS,	ΙΤ,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,
		ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,
		GH,	GM,	KΕ,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,
		,	- ,	,	,	- ,	ТJ,										
ΑU	2007	2469	13		A1		2007	1115		AU 2	007-	2469	13		2	0070	405
CP	2648	487			A1		2007	1115		CA 2	007-	2648	487		2	0070	405
EF	2004	681			A1		2008	1224		EP 2	007-	7323.	29		2	0070	405
	R:	ΑT,	BE,	ВG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	IE,
							LV,										
	2009						2009								_		
	1013						2009									0800	827
	2008						2008									0081	
	2008						2008									0081	
IN	2008	KN04	414		Α		2009	0306		IN 2	0.08 - 1	KN44	14		2	0081	103
	2010				A1		2010	0211			009-					0090	-
PRIORII	Y APP	LN.	INFO	.:						GB 2	006-	6946		-	A 2	0060	406

The invention provides nucleic acid mols. encoding the circularly permuted AΒ human growth hormone GHCP07 and variants thereof, wherein variants contain amino acid changes at the receptor binding sites and acts as growth hormone receptor antagonists. The invention also provides the amino acid sequences of GHCP07, and antagonist GHCP07C, wherein GHCP07C contains a C-terminal region of human growth hormone (GH) linked to a N-terminal region of GH, with a changes in amino acids at receptor binding sites, such as Glycine to Arginine at position 176. The invention further provides various fusion proteins comprised of: (a) at least two GHCP07C polypeptides linked in tandem; (b) extracellular binding domains of growth hormone receptor (GHR) linked to at least two GHCP07 polypeptides; (c) GHCP07C polypeptides linked to a human prolactin modified polypeptide (such as G129R PRL); and/or (d) GHCP07C-human modified prolactin fusions containing an extracellular domain of receptors, such as cytokine, GH, prolactin receptors. The invention was based on the general knowledge that the G129R mutation in PRL and G120R mutation in GH disrupt the structural integrity of the two receptor sites, and results in proteins acting as receptor antagonists. Still further, the invention provides: (a) nucleic acid mols. encoding the disclosed fusion proteins and their use in construction of vectors for recombinant protein production; and (b) the amino acid sequences of said extracellilar domains found in human GHR and the modified $\bar{h}uman$ prolactin (G129R). Finally, the invention provides for the use of the disclosed antagonists, and/or their fusion proteins, and/or their nucleic acids in construction of a pharmaceutical compn which can be use to treat various conditions, such as gigantism, acromegaly, cancer, diabetic retinopathy, diabetic nephropathy and/or other complications of diabetes and/or GH excess. In the examples, the invention presented mol. genetics methods used to generate circularly permutated growth hormone antagonists GHCP07BHis and GHCP07C, and showed that both proteins had antagonistic activity.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2007527470 MEDLINE DOCUMENT NUMBER: PubMed ID: 17721547

TITLE: A ligand-receptor fusion of growth

hormone forms a dimer and is a potent long-acting

agonist.

AUTHOR: Wilkinson Ian R; Ferrandis Eric; Artymiuk Peter J

; Teillot Marc; Soulard Chantal; Touvay Caroline;

Pradhananga Sarbendra L; Justice Sue; Wu Zida; Leung Kin C;

Strasburger Christian J; Sayers Jon R; Ross Richard J

CORPORATE SOURCE: School of Medicine and Biomedical Sciences, Royal

Hallamshire Hospital, University of Sheffield, Sheffield

S10 2JF, UK.

SOURCE: Nature medicine, (2007 Sep) Vol. 13, No. 9, pp. 1108-13.

Electronic Publication: 2007-08-26.

Journal code: 9502015. ISSN: 1078-8956. L-ISSN: 1078-8956.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200803

ENTRY DATE: Entered STN: 11 Sep 2007

Last Updated on STN: 13 Mar 2008

Entered Medline: 12 Mar 2008

Cytokine hormones have a short plasma half-life and require frequent AB administration. For example, growth hormone replacement involves daily injections. In common with other cytokines, the extracellular domain of the growth hormone receptor circulates as a binding protein, which naturally prolongs the biological half-life of growth hormone. Here we have studied the biological actions of a ligand-receptor fusion of growth hormone and the extracellular domain of its receptor. The genetically engineered ligand-receptor fusion protein was purified from mammalian cell culture. In rats, the ligand-receptor fusion had a 300-times reduced clearance as compared to native growth hormone, and a single injection promoted growth for 10 d, far exceeding the growth seen after administration of native growth hormone. The ligand-receptor fusion forms a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone similar to the natural reservoir of growth hormone and its binding protein. In conclusion, a ligand-receptor fusion of cytokine to its extracellular receptor generates a potent, long-acting agonist with exceptionally slow absorption and elimination. This approach could be easily applied to other cytokines.

L6 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:104499 CAPLUS

DOCUMENT NUMBER: 144:219144

TITLE: Recombinant dimers of cytokine receptor-binding

domains linked by inflexible helical linkers for

modulation of cytokine signaling

INVENTOR(S):
Artymiuk, Peter; Pradhananga, Sarbendra;

Sayers, John; Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

	TENT				KIN	D	DATE			APPL:						ATE	
	2006 2006 2006	0108	91 91		A9		2006 2006 2006	0202 0427		WO 2						0050	
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
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		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,
		NG,	ΝI,	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,
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		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	GH,
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		KG,	KΖ,	MD,	RU,	ΤJ,	TM										
ΑU	2005	2661	84		A1		2006	0202		AU 2	005-	2661	84		2	0050	718
CA	2575	441			A1		2006	0202	1	CA 2	005-	2575	441		2	0050	718
EΡ	1771	467			A2		2007	0411		EP 2	005-	7615	93		2	0050	718
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		IS,	ΙT,	LI,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR	

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CN 101014616 A 20070808 CN 2005-80030121 20050718
JP 2008507292 T 20080313 JP 2007-523141 20050718
NZ 553224 A 20090531 NZ 2005-553224 20050718
RU 2391353 C2 20100610 RU 2007-106043 20050718
MX 2007001180 A 20070413 MX 2007-1180 20070126
KR 2007067678 A 20070628 KR 2007-703976 20070220
KR 891509 B1 20090406
IN 2007KN00631 A 20070706 IN 2007-KN631 20070221
KR 2009006221 A 20090114 KR 2008-729058 20081127
US 20090221477 A1 20090903 US 2009-658526 20090416
PRIORITY APPLN. INFO.:

PRIORITY APPLN. INFO.:

RE 2005-2839 A 20050211
WO 2005-GB2826 W 20050718
KR 2007-703976 A3 20070220
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB We disclose therapeutic proteins comprising at least two domains capable of binding to a cytokine receptor, wherein the domains are connected by a peptide linker, wherein the linker optionally comprises a rigid alpha helical region. These proteins may act as agonists or antagonists of cytokine signaling. Thus, growth hormone receptor-binding growth hormone fragments were dimerized using a rigid or semi-rigid linker. The rigid linker comprised the motif A(EAAAK)nA, with n = 1-5 preferred. These proteins were produced with transgenic E. coli. The growth hormone activity of these proteins was equal to or greater than growth hormone itself.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD

(3 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:878488 CAPLUS

DOCUMENT NUMBER: 141:344597

TITLE: Chimeric proteins containing cytokine receptor binding

domain and glycosylphosphatidylinositol anchor and

their therapeutic uses

INVENTOR(S): Ross, Richard; Sayers, Jon; Artymiuk, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PAT	TENT I				KIN	D	DATE			APPL	ICAT	ION I	. O <i>V</i>		D	ATE	
	2004	000-	35		A2 A3		2004 2005			WO 2	004-	GB15	72		2	0040	407
	W:	ΑE,	AG, AL CO, CR		AM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KP,	KR,	KΖ,	LC,
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NΙ,
		NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
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		ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	ΙT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,
		SK,	TR,	BF,	ΒJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,

TD, TG

20060118 EP 1616010 EP 2004-726219 Α2 20040407 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

JP 2007527695 T 20071004 JP 2006-506114 20040407 US 20060205926 Α1 20060914 US 2005-552388 20051007

US 7625998 В2 20091201

PRIORITY APPLN. INFO.: GB 2003-8088 A 20030409 GB 2003-24235 A 20031016

> WO 2004-GB1572 W 20040407

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The present invention relates to polypeptides which comprise a

ligand-binding domain of a cytokine receptor fused with a signal sequence for the attachment of glycosylphosphatidylinositol (GPI) anchors. GPI-anchors are post-translational modifications to proteins that add glycosylphosphatidylinositol which enable these proteins to anchor to the extracellular side of cell membranes. 1B1-GP1 was constructed, in which GH was linked through its C-terminus to the extracellular domain of the GH receptor and then linked to the GPI signal sequence. 1C1-GPI was also constructed, in which a tandem of GH was linked through the second GH C-terminus to the GPI signal sequence. The invention provides vectors and CHO-K1 cells for expressing GHBP-GPI.

THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD OS.CITING REF COUNT: 1

(1 CITINGS)

REFERENCE COUNT: THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 16 BIOSIS COPYRIGHT (c) 2010 The Thomson Corporation on

2004:225928 BIOSIS ACCESSION NUMBER:

DOCUMENT NUMBER: PREV200400225966

TITLE: Tandem fusions of growth hormone and

its G120R mutated antagonist retain biological activity and

demonstrate prolonged plasma half-life.

Pradhananga, S. L. [Reprint Author]; Wilkinson, I. [Reprint AUTHOR(S):

Author]; Haylor, J. [Reprint Author]; Rezaee, S. [Reprint

Author]; Artymiuk, P.; Sayers, J.; Ross, R. J. M.

[Reprint Author]

CORPORATE SOURCE: Department of Clinical Sciences, Sheffield University,

Sheffield, UK

SOURCE: Growth Hormone & IGF Research, (April 2004) Vol. 14, No. 2,

pp. 116. print.

Meeting Info.: Second International GH-IGF Symposium.

Queensland, Australia. April 18-22, 2004.

ISSN: 1096-6374 (ISSN print).

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

English LANGUAGE:

ENTRY DATE: Entered STN: 21 Apr 2004

Last Updated on STN: 21 Apr 2004

ANSWER 15 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:591215 CAPLUS

DOCUMENT NUMBER: 139:144956

TITLE: Ligand binding domains of cytokine which are linked via flexible polypeptide linker and uses in therapy

INVENTOR(S):

Ross, Richard; Artymiuk, Peter; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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KIND DATE APPLICATION NO. DATE
     PATENT NO.
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     WO 2003062276 A2 20030731 WO 2003-GB253 WO 2003062276 A3 20031016
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A2 20041020 EP 2003-702702 20030124
     CA 2510751
     EP 1468020
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20080527 RU 2004-121969
20050331 MX 2004-7160
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     RU 2325400
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     MX 2004007160
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A1
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                                              US 2005-502344
                                                                       20050511
                                                                  A 20020125
PRIORITY APPLN. INFO.:
                                              GB 2002-1679
                                                              W 20030124
                                              WO 2003-GB253
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The invention relates to the provision of oligomeric polypeptides (dimers, trimers, etc) comprising the ligand binding domains of cytokines which are linked via flexible polypeptide linker mols. The linker mols. optionally comprise protease sensitive sites to modulate the release of biol. active cytokines when administered to a human or animal subject. The invention also relates to chemical crosslinkers wherein the chemical crosslinkers serve

link the ligand binding domains. The chimeric cytokine can be used for treating acromegaly, gigantism, GH deficiency, Turners syndrome, renal failure, osteoporosis, diabetes mellitus, cancer, obesity, insulin resistance, hyperlipidemia, hypertension, anemia, autoimmune and

infectious disease, inflammatory disorders including rheumatoid arthritis. OS.CITING REF COUNT: THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 16 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

2001:924005 CAPLUS ACCESSION NUMBER:

136:49347 DOCUMENT NUMBER:

TITLE: Chimeric binding agent comprising cytokine, linker and

cytokine receptor and uses in modulating receptor

activity and therapy

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

Asterion Limited, UK PATENT ASSIGNEE(S): SOURCE: PCT Int. Appl., 79 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

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PATENT NO.
                         KIND DATE
                                         APPLICATION NO. DATE
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                                              _____
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     WO 2001096565 A2 20011220 WO 2001-GB2645 WO 2001096565 A3 20020801
                                                                      20010618
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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              GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
              LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
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                          A1 20011220 CA 2001-2447632 20010618
A2 20030312 EP 2001-940731 20010618
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     EP 1290170
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     JP 2004503243 T 20040205 JP 2002-510682
US 20040071655 A1 20040415 US 2003-311473
US 7446183 B2 20081104
US 20090054336 A1 20090226 US 2008-175582
                                                                       20010618
                                                                       20030718
                                              US 2008-175582 20080718
GB 2000-14765 A 20000616
GB 2001-5969 A 20010310
GB 2001-6487 A 20010316
WO 2001-GB2645 W 20010618
                                                                       20080718
PRIORITY APPLN. INFO.:
                                               US 2003-311473 A1 20030718
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
     The invention provides a binding agent comprising a first part capable of
     binding a ligand binding domain of a receptor linked to a second part
     comprising a receptor binding domain wherein said binding agent modulates
     the activity of the receptor. The inventors link growth
     hormone (GH), through its C-terminal and a linker to the
     N-terminus of the SD100 domain of growth hormone
     receptor (GHR). By varying the length of the linker inventors define a
     mol. that has the flexibility to allow binding of GH through site 1 to
     full length receptor at the cell surface. The invention also relates to
     methods, vectors and host cells for production of said chimeric binding agent.
OS.CITING REF COUNT:
                                 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD
                                 (6 CITINGS)
REFERENCE COUNT:
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L2
L3
             19 DUP REM L2 (3 DUPLICATES REMOVED)
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L4
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L5
              16 DUP REM L5 (3 DUPLICATES REMOVED)
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          11282 S ROSS R?/AU
L7
L8
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L9
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L10
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FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 15:09:50 ON 28 JUN 2010

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L10 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:1048978 CAPLUS

DOCUMENT NUMBER: 151:307229

TITLE: Linker peptides including glycosylation sites for use

in fusion proteins

Artymiuk, Peter; Ross, Richard; Sayers, Jon INVENTOR(S):

Asterion Limited, UK PCT Int. Appl., 185pp. PATENT ASSIGNEE(S): SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	ENT	.OV			KIN	D	DATE			APPL	ICAT	ION I	NO.		D	ATE	
WO	2009	1039	 65		A1		 2009	0827	-	wo 2	009-	 GB43	7		2	0090	218
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PRIORITY	APP	LN.	INFO	.:					1	GB 2	008-	2978			A 2	0080	219
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									1	GB 2	009-	539			A 2	0090	114

OTHER SOURCE(S): MARPAT 151:307229

Peptide linkers that contain a glycosylation site and that can be used in the manufacture of fusion proteins that interact with membranes, e.g. fusion proteins of proteins and their cognate receptors. Glycosylation site

motif variants for use in linker peptides are described.

REFERENCE COUNT: THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS 6 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2009:115655 CAPLUS

DOCUMENT NUMBER: 150:161106

Growth hormone fusion proteins

Ross, Richard; Artymiuk, Peter; Sayers, Jon Asterion Limited, UK INVENTOR(S):

PATENT ASSIGNEE(S): PCT Int. Appl., 41pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE: Patent English LANGUAGE:

PA.	TENT :	NO.			KIN	D	DATE								D	ATE	
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AU	2008	2789	07		A1		2009	0129		AU 2	008 -	2789	07		2	0080	716
CA	2693	951			A1		2009	0129		CA 2	0.08 -	2693	951		2	0080	716
EP	2170	943			A1		2010	0407		EP 2	008-	7759	45		2	0080	716
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AB We disclose growth hormone fusion proteins that have increased in vivo stability and activity; nucleic acid mols. encoding said proteins and methods of treatment of growth hormone deficiency that use said proteins. This disclosure relates to the biol. actions of a ligand-receptor fusion (LR-fusion) of GH with its extracellular domain receptor. Such a genetically engineered LR-fusion protein was purified from mammalian cell culture. In rats the LR-fusion had a 300-times reduced clearance compared to native GH and single administration promoted growth for 10 days far superior to that seen with native GH. The reduced clearance is reproducible in a primate model. The LR-fusion forms a reciprocal, head-to-tail dimer that provides a reservoir of inactive hormone as occurs naturally with GH and its binding protein. A recombinant gene encoding human GH linked to the A & B domains of the GHR extracellular domain (exGHR1-238) via a flexible (Gly4Ser)4 linker, was generated (Fig. 1 c).

REFERENCE COUNT:

INVENTOR(S):

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L10 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
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ACCESSION NUMBER: 2007:1303035 CAPLUS

DOCUMENT NUMBER: 147:535195

TITLE: Fusion protein composed of circularly permuted

growth hormone antagonist GHCP07C,

extracellular domain of receptor, and human modified

prolactin, and its use in construction of

pharmaceutical compositions for treating disorders

Pradhananga, Sarbendra; Sayers, John; Ross,

Richard; Artymiuk, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 46pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PAT	ENT I	. O <i>l</i> .			KIND DATE				APPI	LICAT		DATE					
	WO	2007	 1289	 79		A1		 2007	1115	1	WO 2	2007-0	GB12	 85		2	0070	405
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			KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	MG,	MK,
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			IS,	ΙΤ,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,
			ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	ΤG,	BW,
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	ΑU	20072	2469	13		A1		2007	1115		AU 2	2007-2	2469	13		2	0070	405
	CA	2648	487			A1		2007	1115	(CA 2	2007-2		2	0070	405		
	EΡ	2004	681			A1		2008	1224		EP 2	2007-		20070405				
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	JΡ	2009!	5320.	51		${f T}$		2009	0910			2009-						
	CN	10138	3964	9		Α		2009	0318	(CN 2	2007-8	3000	6944		2	0080	827
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	MX	2008	0129:	34		А		2008	1015]	MX 2	2008-1	1293	4		2	0081	006
	ΙN	20081	KN04	414		Α		2009	0306		IN 2	1 - 8009	KN44	14		2	0081	103
	US	2010	0035	804		A1		2010	0211			2009-2						
PRIO	RITY	APP	LN.	INFO	.:							2006-6						
	m1										-	2007-0	-				0070	

AΒ The invention provides nucleic acid mols. encoding the circularly permuted human growth hormone GHCP07 and variants thereof, wherein variants contain amino acid changes at the receptor binding sites and acts as growth hormone receptor antagonists. The invention also provides the amino acid sequences of GHCP07, and antagonist GHCP07C, wherein GHCP07C contains a C-terminal region of human growth hormone (GH) linked to a N-terminal region of GH, with a changes in amino acids at receptor binding sites, such as Glycine to Arginine at position 176. The invention further provides various fusion proteins comprised of: (a) at least two GHCP07C polypeptides linked in tandem; (b) extracellular binding domains of growth hormone receptor (GHR) linked to at least two GHCP07 polypeptides; (c) GHCP07C polypeptides linked to a human prolactin modified polypeptide (such as G129R PRL); and/or (d) GHCP07C-human modified prolactin fusions containing an extracellular domain of receptors, such as cytokine, GH, prolactin receptors. The invention was based on the general knowledge that the G129R mutation in PRL and G120R mutation in GH disrupt the structural integrity of the two receptor sites, and results in proteins acting as receptor antagonists. Still further, the invention provides: (a) nucleic acid mols. encoding the disclosed fusion proteins and their use in construction of vectors for recombinant protein production; and (b) the amino acid sequences of said extracellilar domains found in human GHR and the modified human prolactin (G129R). Finally, the invention provides for the use of the disclosed antagonists, and/or their fusion proteins, and/or their nucleic acids in construction of a pharmaceutical compn which can be use to treat various conditions, such as gigantism, acromegaly, cancer, diabetic retinopathy, diabetic nephropathy and/or other complications of diabetes and/or GH excess. In the examples, the invention presented mol. genetics methods used to generate circularly permutated growth

hormone antagonists GHCP07BHis and GHCP07C, and showed that both proteins had antagonistic activity.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2007527470 MEDLINE DOCUMENT NUMBER: PubMed ID: 17721547

TITLE: A ligand-receptor fusion of growth

hormone forms a dimer and is a potent long-acting

agonist.

AUTHOR: Wilkinson Ian R; Ferrandis Eric; Artymiuk Peter J; Teillot

Marc; Soulard Chantal; Touvay Caroline; Pradhananga

Sarbendra L; Justice Sue; Wu Zida; Leung Kin C; Strasburger

Christian J; Sayers Jon R; Ross Richard J

CORPORATE SOURCE: School of Medicine and Biomedical Sciences, Royal

Hallamshire Hospital, University of Sheffield, Sheffield

S10 2JF, UK.

SOURCE: Nature medicine, (2007 Sep) Vol. 13, No. 9, pp. 1108-13.

Electronic Publication: 2007-08-26.

Journal code: 9502015. ISSN: 1078-8956. L-ISSN: 1078-8956.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200803

ENTRY DATE: Entered STN: 11 Sep 2007

Last Updated on STN: 13 Mar 2008 Entered Medline: 12 Mar 2008

AB Cytokine hormones have a short plasma half-life and require frequent

administration. For example, growth hormone

replacement involves daily injections. In common with other cytokines,

the extracellular domain of the growth hormone

receptor circulates as a binding protein, which naturally prolongs the

biological half-life of growth hormone. Here we have

studied the biological actions of a ligand-receptor fusion of

growth hormone and the extracellular domain of its

receptor. The genetically engineered ligand-receptor fusion

protein was purified from mammalian cell culture. In rats, the

ligand-receptor fusion had a 300-times reduced clearance as

compared to native growth hormone, and a single

injection promoted growth for 10 d, far exceeding the growth seen after

administration of native growth hormone. The

ligand-receptor fusion forms a reciprocal, head-to-tail dimer that

provides a reservoir of inactive hormone similar to the natural reservoir of growth hormone and its binding protein. In

conclusion, a ligand-receptor fusion of cytokine to its

extracellular receptor generates a potent, long-acting agonist with exceptionally slow absorption and elimination. This approach could be

easily applied to other cytokines.

L10 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2006:104499 CAPLUS

DOCUMENT NUMBER: 144:219144

TITLE: Recombinant dimers of cytokine receptor-binding

domains linked by inflexible helical linkers for

modulation of cytokine signaling

INVENTOR(S): Artymiuk, Peter; Pradhananga, Sarbendra; Sayers, John;

Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	CENT				KIN:	D	DATE			APPLICATION NO.								
WO WO	2006 2006 2006	0108 0108	91 91		A2			0202 0427		WO 2	2005-	 GB28				0050	718	
NO	W:	AE, CN, GE, LC, NG, SL, ZA, CG, AT, IS, CF,	AG, CO, GH, LK, NI, SM, ZM, CI, BE, IT, CG,	AL, CR, GM, LR, NO, SY, ZW, CM, BG, LT, CI,	AM, CU, HR, LS, NZ, TJ, SZ, GA, CH, LU, CM,	AT, CZ, HU, LT, OM, TM, BE, GN, CY, LV,	AU, DE, ID, LU, PG, TN, CY, GQ, CZ, MC, GN,	AZ, DK, IL, LV, PH, TR, FR, GW, DE, NL, GQ,	DM, IN, MA, PL, TT, GR, ML, DK, PL, GW,	DZ, IS, MD, PT, IE, MR, EE, PT,	BG, EC, JP, MG, RO, UA, IT, NE, ES, RO,	EE, KE, MK, RU, UG, MC, SN, FI, SE, NE,	EG, KG, MN, SC, US, NL, TD, FR, SI, SN,	ES, KM, MW, SD, UZ, SI, TG GB, SK, TD,	FI, KP, MX, SE, VC, BF, GR, TR,	GB, KR, MZ, SG, VN, BJ, HU, BF, BW,	GD, KZ, NA, SK, YU, CF, IE, BJ, GH,	
CA EP CN JP NZ RU MX KR KR IN KR US PRIORITY		KG, 2661 441 467 AT, 1861 5072 24 353 0011 0676 09 KN00 0062 0221 LN.	KZ, 84 BE, IT, 692 80 78 631 21 477 INFO	MD, BG, LI,	A1 A2 CH, LT, A C2 A B1 A A1	TJ,	TM 2006 2007 CZ, LV, 2007 2008 2009 2010 2007 2007 2009 2007	0202 0202 0411 DE, MC, 0808 0313 0531 0610 0413 0628 0406 0706 0114 0903	DK, NL,	AU 2 CA 2 EP 2 PL, CN 2 JP 3 NZ 2 RU 3 KR 2 US 3 GB 3 WO 3 KR 3	2005- 2005- 2005- ES, PT, 2005- 2007- 2007- 2007- 2007- 2004- 2004- 2005- 2005- 2005- 2007-	2661 2575 7615 FI, 8003 5532 1060 1180 7039 KN63 7290 6585 5913 1668 2839 GB28	84 441 93 FR, SE, 0121 41 24 43 76 1 58 26 58P 7	GB, SI,	2 2 2 3 3 5 4 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	0050 0050 0050 HU,	718 718 718 718 718 718 718 718 726 727 416 726 727 211 718	
ASSIGNME	ENT H	ISTO	RY F	OR U	S PA'	TEN]	AVA	ILAB	LE I	N LS	SUS D	ISPL.	AY F	ORMA	T			

AΒ We disclose therapeutic proteins comprising at least two domains capable of binding to a cytokine receptor, wherein the domains are connected by a peptide linker, wherein the linker optionally comprises a rigid alpha helical region. These proteins may act as agonists or antagonists of cytokine signaling. Thus, growth hormone receptor-binding growth hormone fragments were dimerized using a rigid or semi-rigid linker. The rigid linker comprised the motif $A(EAAAK)\,nA$, with n=1-5 preferred. These proteins were produced with transgenic E. coli. The growth hormone activity of these proteins was equal to or greater than growth hormone itself.

THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD OS.CITING REF COUNT: 3 (3 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2006194908 MEDLINE DOCUMENT NUMBER: PubMed ID: 16464942

TITLE: A mutant signal transducer and activator of transcription

5b, associated with growth hormone

insensitivity and insulin-like growth factor-I deficiency, cannot function as a signal transducer or transcription $% \left(1\right) =\left(1\right) \left(1\right) \left$

factor.

AUTHOR: Fang Peng; Kofoed Eric M; Little Brian M; Wang Xiangdong;

Ross Richard J M; Frank Stuart J; Hwa Vivian;

Rosenfeld Ron G

CORPORATE SOURCE: Department of Pediatrics, NRC5, Oregon Health and Science

University, 3181 Southwest Sam Jackson Park Road, Portland,

OR 97239-3098, USA.

CONTRACT NUMBER: CA 58110 (United States NCI NIH HHS)

DK 46395 (United States NIDDK NIH HHS)

SOURCE: The Journal of clinical endocrinology and metabolism, (2006

Apr) Vol. 91, No. 4, pp. 1526-34. Electronic Publication:

2006-02-07.

Journal code: 0375362. ISSN: 0021-972X. L-ISSN: 0021-972X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)

(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200605

ENTRY DATE: Entered STN: 8 Apr 2006

Last Updated on STN: 2 May 2006 Entered Medline: 1 May 2006

AΒ CONTEXT: A natural missense mutation in the signal transducer and activator of transcription (STAT) 5b gene was recently identified in association with a female patient presenting with severe growth failure and immune dysfunction. The mutation results in an alanine to proline substitution at residue 630 (A630P) in the src-homology-2 domain, a region essential for docking of STATs to phospho-tyrosines on activated receptors, STAT dimerization, and stabilization of phospho-STAT-DNA interactions. OBJECTIVE: The purpose of this study was to explore the molecular mechanisms underlying the GH insensitivity and IGF-I deficiency caused by the A630P-mutated STAT5b. RESULTS: In reconstitution experiments using HEK293 cells, both GH and interferon-gamma were unable to activate mutant STAT5b (A630P), as demonstrated by lack of immunodetectable phospho-tyrosyl-STAT5b (A630P) and inability to drive luciferase reporter activity. However, the Src family of nonreceptor kinases [constitutively active v-src and epithelial growth factor-induced c-src] tyrosine-phosphorylated STAT5b(A630P). The v-src-induced phospho-STAT5b(A630P) translocated to the nucleus but, unlike wild-type Stat5b, was unable to bind DNA. CONCLUSIONS: The A630P mutation disrupts the src-homology-2 architecture such that: 1) mutant STAT5b most likely cannot dock to phospho-tyrosines on ligand-activated receptors; and 2) stable interactions with DNA are prevented. Because STAT5b (A630P) is an inefficient signal transducer and transcription factor, the detrimental impact on signaling pathways important for normal growth and immunity explains, in part, the complex clinical phenotype of GH insensitivity and immune dysfunction.

ACCESSION NUMBER: 2006076164 MEDLINE DOCUMENT NUMBER: PubMed ID: 16461551

TITLE: A 36 residues insertion in the dimerization domain of the

growth hormone receptor results in

defective trafficking rather than impaired signaling.

AUTHOR:

Maamra M; Milward A; Esfahani H Zarkesh; Abbott L P;

Metherell L A; Savage M O; Clark A J L; Ross R J M

COPPORATE SOURCE:

Division of Clinical Sciences (North) University of

CORPORATE SOURCE: Division of Clinical Sciences (North), University of

Sheffield, Clinical Sciences Centre, Northern General

Hospital, Sheffield S5 7AU, UK.

SOURCE: The Journal of endocrinology, (2006 Feb) Vol. 188, No. 2,

pp. 251-61.

Journal code: 0375363. ISSN: 0022-0795. L-ISSN: 0022-0795.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200604

ENTRY DATE: Entered STN: 8 Feb 2006

Last Updated on STN: 5 Apr 2006 Entered Medline: 4 Apr 2006

Growth hormone insensitivity syndrome (GHIS) has been AΒ reported in a family homozygous for a point mutation in the GH receptor (GHR) that activates an intronic pseudoexon. The resultant GHR (GHR1-656) includes a 36 amino-acids insertion after residue 207, in the region known to be important for homodimerization of GHR. We have examined the functional consequences of such an insertion in mammalian cells transfected with the wild type (GHRwt) and mutated GHR (GHR1-656). ligand binding and flow cytometry analysis showed that GHR1-656 is poorly expressed at the cell surface compared with GHRwt. Total membrane binding and Western blot analysis showed no such difference in the level of total cellular GHR expressed for GHR1-656 vs GHRwt. Immunofluorescence showed GHR1-656 to have different cellular distribution to the wild type receptor (GHRwt), with the mutated GHR being mainly perinuclear and less vesicular than GHRwt. Western blot analysis showed GH-induced phosphorylation of Jak2 and Stat5 for both GHR1-656 and GHRwt, although reduced Stat5 activity was detected with GHR1-656, consistent with lower levels of expression of GHR1-656 than GHRwt at the cell surface. In conclusion, we report that GHIS, due to a 36 amino-acids insertion in the extracellular domain of GHR, is likely to be explained by a trafficking defect rather than by a signalling defect of GHR.

L10 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2005:34776 CAPLUS

DOCUMENT NUMBER: 142:127937

TITLE: Modified cytokine ligand polypeptides

preparation, screening, and uses thereof for treatment

INVENTOR(S): Sayers, Jon; Artymuik, Peter; Ross, Richard

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005003165 WO 2005003165	A2 A3	20050113 20050714	WO 2004-GB2827	20040628

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             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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                         A2 20060329 EP 2004-743175
B1 20100505
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                                                                     20040628
     EP 1639002
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     JP 2008504001 T 20080214 JP 2006-518330 20040628
AT 466880 T 20100515 AT 2004-743175 20040628
US 20070264234 A1 20071115 US 2007-561831 20070316
RITY APPLN. INFO:: GB 2003-15182 A 20030628
WO 2004-GB2827 W 20040628
                                                               2007051
A 20030628
20040628
PRIORITY APPLN. INFO.:
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
     The disclosed invention describes modified cytokine liqand
     polypeptides comprising a modified amino acid sequence which is a
     modification of the native cytokine amino acid sequence of said
     ligand, wherein the native N terminal and C terminal amino acid
     residues of the native polypeptide are linked, directly or indirectly,
     together, characterized in that said ligand is provided with
     alternative N terminal and C terminal amino acid residues and further
     wherein at least one binding domain for said ligand's cognate
     binding partner or receptor complex is disrupted. The authors describe
     the first embodiment of the growth hormone circular
     permutation GH CP01, with the N terminus Ile121 and the C terminus Glu118.
     The "old" termini of GH were linked by a 6 amino acid linker, formed by
     joining the "old" termini -3 amino acids from the first helix at the N
     terminus and +3 residues for the last helix at the C terminus. E. coli
     cells were used as the expression system. Also described are alternative
     approaches to construct circular permutations of GH.
OS.CITING REF COUNT:
                                THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
                                (2 CITINGS)
                                THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L10 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:
                         2004:878488 CAPLUS
DOCUMENT NUMBER:
                          141:344597
TITLE:
                          Chimeric proteins containing cytokine receptor binding
                          domain and glycosylphosphatidylinositol anchor and
                          their therapeutic uses
                          Ross, Richard; Sayers, Jon; Artymiuk, Peter
INVENTOR(S):
PATENT ASSIGNEE(S):
                        Asterion Limited, UK
                          PCT Int. Appl., 40 pp.
SOURCE:
                          CODEN: PIXXD2
DOCUMENT TYPE:
                          Patent
                          English
LANGUAGE:
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
     PATENT NO.
                        KIND DATE APPLICATION NO. DATE
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WO 2004090135 A2 20041021 WO 2004-GB1572 20040407

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WO 2004090135
                                20050428
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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             TD, TG
     EP 1616010
                          Α2
                                20060118
                                            EP 2004-726219
                                                                   20040407
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     JP 2007527695
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                                20071004
                                           JP 2006-506114
                                                                   20040407
     US 20060205926
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                                20091201
PRIORITY APPLN. INFO.:
                                            GB 2003-8088
                                                                A 20030409
                                            GB 2003-24235
                                                                   20031016
                                                                Α
                                            WO 2004-GB1572
                                                                W
                                                                   20040407
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
     The present invention relates to polypeptides which comprise a
     ligand-binding domain of a cytokine receptor fused with a signal
     sequence for the attachment of glycosylphosphatidylinositol (GPI) anchors.
     GPI-anchors are post-translational modifications to proteins that add
     glycosylphosphatidylinositol which enable these proteins to anchor to the
     extracellular side of cell membranes. 1B1-GP1 was constructed, in which
     GH was linked through its C-terminus to the extracellular domain of the GH
     receptor and then linked to the GPI signal sequence. 1C1-GPI was also
     constructed, in which a tandem of GH was linked through the second GH
     C-terminus to the GPI signal sequence. The invention provides vectors and
     CHO-K1 cells for expressing GHBP-GPI.
OS.CITING REF COUNT:
                               THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
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                               (1 CITINGS)
REFERENCE COUNT:
                         5
                               THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L10 ANSWER 10 OF 16
                        MEDLINE on STN
                                                        DUPLICATE 3
ACCESSION NUMBER:
                    2004448217
                                   MEDLINE
DOCUMENT NUMBER:
                    PubMed ID: 15356058
TITLE:
                    Pegvisomant, a growth hormone-specific
                    antagonist, undergoes cellular internalization.
AUTHOR:
                    Maamra M; Kopchick J J; Strasburger C J; Ross R J M
                    Sheffield University, Clinical Sciences, Northern General
CORPORATE SOURCE:
                    Hospital, Sheffield, United Kingdom.
                    The Journal of clinical endocrinology and metabolism, (2004
SOURCE:
                    Sep) Vol. 89, No. 9, pp. 4532-7.
                    Journal code: 0375362. ISSN: 0021-972X. L-ISSN: 0021-972X.
                    United States
PUB. COUNTRY:
DOCUMENT TYPE:
                    Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:
                    English
                    Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT:
ENTRY MONTH:
                    200410
ENTRY DATE:
                    Entered STN: 10 Sep 2004
                    Last Updated on STN: 8 Oct 2004
                    Entered Medline: 7 Oct 2004
     GH binding to a receptor (GHR) dimer triggers signaling and
AΒ
     internalization of the receptor/ligand complex. Pegvisomant is
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a specific GH antagonist developed for the treatment of acromegaly, and

the basic molecule is GH with an amino acid substitution that blocks the conformational change necessary to generate functional GHR dimerization required for signal transduction. Pegvisomant has additional polyethylene glycol moieties to prolong its half-life in the circulation and improve clinical efficacy through reduced renal clearance. Pegvisomant has a long plasma half-life, and its mode of clearance has not been established. We have studied pegvisomant internalization and demonstrate that despite its size and prolonged plasma half-life, it is internalized by cells expressing the GHR. As pegvisomant does not activate intracellular signal transduction systems, our results support the concept that the conformational changes required for GHR signaling are not essential for the intracellular trafficking of the ligand and establish one potential contributing mechanism for pegvisomant clearance.

L10 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:591215 CAPLUS

DOCUMENT NUMBER: 139:144956

TITLE: Ligand binding domains of cytokine which are

linked via flexible polypeptide linker and uses in

therapy

INVENTOR(S): Ross, Richard; Artymiuk, Peter; Sayers, Jon

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	ATE	I TN	OV.			KIND DATE				APPI	LICAT	ION 1	DATE							
			 0622 0622			A2 20030731 A3 20031016				WO 2	2003-		20030124							
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			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,	LK,	LR,		
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			PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	ΤJ,	TM,	TN,	TR,	TT,	TZ,		
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J:	JP 2005529583							2005	1006		JP 2	2003-		2	0030	124				
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U	S 2	0050	0214	762		A1	A1 20050929			US 2005-502344					20050511					
PRIORI'	TY	APP1	LN.	INFO	.:					GB 2002-1679					1	A 20020125				
											WO 2	2003-0	GB25	3		W 2	0030	124		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The invention relates to the provision of oligomeric polypeptides (dimers, trimers, etc) comprising the ligand binding domains of cytokines which are linked via flexible polypeptide linker mols. The linker mols. optionally comprise protease sensitive sites to modulate the release of biol. active cytokines when administered to a human or animal subject. The invention also relates to chemical crosslinkers wherein the chemical

crosslinkers serve to link the ligand binding domains. The chimeric cytokine can be used for treating acromegaly, gigantism, GH deficiency, Turners syndrome, renal failure, osteoporosis, diabetes mellitus, cancer, obesity, insulin resistance, hyperlipidemia, hypertension, anemia, autoimmune and infectious disease, inflammatory disorders including rheumatoid arthritis.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2004:180984 CAPLUS

DOCUMENT NUMBER: 140:194483

TITLE: Chimeric proteins containing cytokine receptor binding

domain and glycosylphosphatidylinositol-containing

signaling peptide and their therapeutic uses

INVENTOR(S): Ross, Richard
PATENT ASSIGNEE(S): Asterion Ltd., UK

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PA:					KIND DATE					LICAT		DATE					
WO	2003	0342	75		A2		2003	0424			2002-				2	0021	011
WO	2003	0342	75		A3		2003	1127									
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											2002-					0021	011

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT AB The present invention relates to polypeptides which comprise a

cytokine-binding domain of a cytokine receptor fused with a signal sequence for the attachment of glycosylphosphatidylinositol (GPI) anchors. The cytokine receptor variants lack a cytoplasmic domain and therefore do not have the capability to signal. The provision of a GPI-anchor domain means the variant inserts into membranes and acts as an effective inhibitor of GH signaling by competing for circulating cytokine and binding cytokine at the cell surface in a heterodimeric complex that consists of the chimeric truncated GPI anchored receptor, cytokine, and the native receptor. In addition, truncated GPI-anchored receptor generates a large amount of soluble receptor which will bind its ligand. In a preferred embodiment, the chimeric protein acts as an antagonist following local or transgenic expression through gene therapy. Thus, the cDNA extracellular domain of human growth hormone receptor (bases 98-834 of GenBank X06562) is ligated into a vector (pAc6-LP-MCS-GPI) containing the Dictyostelium actin 6 gene promoter, a Dictyostelium signal peptide coding region, multiple, cloning site, and the signal for a GPI anchor, and the construct is transfected into Dicytostelium cells. To demonstrate that growth hormone receptor-GPI can act as a transgenic therapy, the extracellular domain of the growth hormone receptor is cloned upstream of a

human GPI signal sequence into a mammalian expression vector.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2003:550165 CAPLUS

DOCUMENT NUMBER: 139:112729

TITLE: Chimeric growth hormone-

growth hormone receptor proteins and

therapeutic uses thereof

INVENTOR(S): Ross, Richard; Sayers, Jon; Artymuik, Peter

PATENT ASSIGNEE(S): Asterion Limited, UK

SOURCE: Brit. UK Pat. Appl., 46 pp.

CODEN: BAXXDU

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT NO.	KIND D	DATE AP	PLICATION NO.			
GB 2384001			3 2001–30052	20011214		
GB 2384001		20040204				
GB 2389115	A 2	20031203 GB	3 2003-20479	20011214		
GB 2389115	B 2	20050316				
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WO 2003070765	A2 2	20030828 WO	2002-GB5523	20021206		
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W: AE, AG, AL,	AM, AT,	AU, AZ, BA, B	BB, BG, BR, BY, BZ	, CA, CH, CN,		
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GM, HR, HU,	ID, IL,	IN, IS, JP, K	E, KG, KP, KR, KZ	, LC, LK, LR,		
LS, LT, LU,	LV, MA,	MD, MG, MK, M	IN, MW, MX, MZ, NO	, NZ, OM, PH,		
PL, PT, RO,	RU, SC,	SD, SE, SG, S	K, SL, TJ, TM, TN	, TR, TT, TZ,		
UA, UG, US,	UZ, VN,	YU, ZA, ZM, Z	W			
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A2 20040915
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IN 2004KN00751 A 20060421

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A1 20080522 AU 2008-201889

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PRIORITY APPLN. INFO.:
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ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A chimeric polypeptide comprising at least one modified binding domain of growth hormone (GH) and a ligand binding domain of growth hormone receptor (GHR) is claimed, wherein the modification is the addition, deletion or substitution of at least one amino acid. Said binding domain may be site 1 of growth hormone, site 2 of growth hormone or both sites of growth hormone. The binding domain of the growth hormone receptor may be the extracellular domain of GHR more preferably the C-terminal SD-100 domain. Nucleic acids encoding such polypeptides, expression vectors and cells expressing such vectors are also claimed. The use of such polypeptides in the preparation of pharmaceuticals and in the treatment of diseases including gigantism, acromegaly, cancer and diabetic conditions is also claimed. Alternatively claimed is a chimeric polypeptide comprising more than two modified growth hormone binding domains.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN ACCESSION NUMBER: 2003:300688 CAPLUS

DOCUMENT NUMBER: 138:315840

Preparation of GPI-anchored proteins with cytokine TITLE:

receptor ligand binding domain and signal

sequence

Ross, Richard INVENTOR(S):

PATENT ASSIGNEE(S): Asterion Limited, UK

SOURCE: Brit. UK Pat. Appl., 41 pp.

CODEN: BAXXDU

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PA:	TENT	NO.			KINI	D	DATE			APP	LICAT		DATE				
CA	2380 2494 2003	706			A 20030416 A1 20030424 A2 20030424			0424		CA			20011013 20021011 20021011				
	2003				A3		2003										
WO	Z005								DΛ	DD	, BG,	DD	DV	D7	C_{λ}	СП	CM
	VV :																
											, EE,						
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							VN,										
	RW:										, TZ,						
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	1568				А						2002-						
			07		Τ		2005	0224		JΡ	2003-	5369	34		2	0021	011
	4384						2009										
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RU	2340	628			C2						2004-					0021	011
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		LI,	LU,	MC,	NL,	PT,	SE,	SK,	TR								
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ASSIGNM	ENT H	ISTO:	RY F	OR U	S PA	TENT	AVA	ILAB	LE I	N L	SUS D	ISPL	AY F	ORMA	Γ		

AB The present invention relates to polypeptides which comprise a receptor binding domain of a cytokine and a domain which includes a signal sequence for the attachment of glycosylphosphhatidylinositol (GPI) anchors. The invention also relates to methods to manufacture the polypeptides, nucleic acids, mols. encoding the polypeptides and therapeutic compns. by comprising the polypeptides.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 2001:924005 CAPLUS

136:49347 DOCUMENT NUMBER:

Chimeric binding agent comprising cytokine, linker and TITLE .

cytokine receptor and uses in modulating receptor

activity and therapy

Ross, Richard; Artymiuk, Peter; Sayers, Jon INVENTOR(S):

PATENT ASSIGNEE(S): Asterion Limited, UK SOURCE: PCT Int. Appl., 79 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA.	TENT	NO.			KINI	O	DATE			APPL	ICAT		DATE				
	2001 2001						2001 2002	_		WO 2	001-	 GB26	45		2	0010	618
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CA	RW:	GH, DE, BJ,	GM, DK, CF,	KE, ES, CG,	FI, CI,	MW, FR, CM,	GB, GA,	GR, GN,	IE, GW,	IT, ML,	LU, MR,	MC, NE,	NL, SN,	PT, TD,	SE, TG	CH, TR,	BF,
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					0 53			T. 7 D.		US 2	001-	3114	73		A1 2	0010 0030	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

The invention provides a binding agent comprising a first part capable of binding a ligand binding domain of a receptor linked to a second part comprising a receptor binding domain wherein said binding agent modulates the activity of the receptor. The inventors link growth hormone (GH), through its C-terminal and a linker to the N-terminus of the SD100 domain of growth hormone receptor (GHR). By varying the length of the linker inventors define a mol. that has the flexibility to allow binding of GH through site 1 to full length receptor at the cell surface. The invention also relates to methods, vectors and host cells for production of said chimeric binding agent.

THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD OS.CITING REF COUNT: 6

(6 CITINGS)

REFERENCE COUNT: THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 1999262630 MEDLINE DOCUMENT NUMBER: PubMed ID: 10329677

TITLE: Studies with a growth hormone

antagonist and dual-fluorescent confocal microscopy

demonstrate that the full-length human growth

hormone receptor, but not the truncated isoform, is

very rapidly internalized independent of Jak2-Stat5

signaling.

AUTHOR: Maamra M; Finidori J; Von Laue S; Simon S; Justice S;

Webster J; Dower S; Ross R

CORPORATE SOURCE: Divisions of Clinical Sciences, Sheffield University,

Sheffield S5 7AU, United Kingdom.

SOURCE: The Journal of biological chemistry, (1999 May 21) Vol.

274, No. 21, pp. 14791-8.

Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907

ENTRY DATE: Entered STN: 27 Jul 1999

Last Updated on STN: 27 Jul 1999 Entered Medline: 9 Jul 1999

AΒ We have investigated trafficking of two negative regulators of growth hormone receptor (GHR) signaling: a human, truncated receptor, GHR1-279, and a GH antagonist, B2036. Fluorescent-labeled growth hormone (GH) was rapidly internalized by the full-length GHR, with >80% of the hormone internalized within 5 min of exposure to GH. In contrast, <5% of labeled GH was internalized by cells expressing truncated GHR1-279. Using another truncated receptor, GHR1-317 fused to enhanced green fluorescent protein (EGFP), we have exploited fluorescence energy transfer to monitor the trafficking of ligand-receptor complexes. The data confirmed that internalization of this truncated receptor is very inefficient. was possible to visualize the truncated GHR1-317-EGFP packaged in the endoplasmic reticulum, its rapid movement in membrane bound vesicles to the Golqi apparatus, and subsequent transport to the cell membrane. The GH antagonist, B2036, blocked Jak2-Stat5-mediated GHR signaling but was internalized with a similar time course to native GH. The results: 1) demonstrate the rapid internalization of GH when studied under physiological conditions; 2) confirm the hypothesis that internalization of cytoplasmic domain truncated human GHRs is very inefficient, which explains their dominant negative action; and 3) show that the antagonist action of B2036 is independent of receptor internalization.

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF